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Full Title: The 'At-Risk Mental State' for psychosis in adolescents: Clinical presentation, transition and remission.

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Running Header: The 'At-Risk Mental State' for psychosis in adolescents

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Abstract:

Despite increased efforts over the last decade to prospectively identify individuals at ultra-high risk of developing a psychotic illness, limited attention has been specifically directed towards adolescent populations (<18 years). In order to evaluate how those under 18 fulfilling the operationalised criteria for an At-Risk Mental State (ARMS) present and fare over time, we conducted an observational study. Participants (N=30) generally reported a high degree of functional disability and frequent and distressing perceptual disturbance, mainly in the form of auditory hallucinations. Seventy percent (21/30) were found to fulfil the criteria for a co-morbid ICD-10 listed mental health disorder, with mood (affective; 13/30) disorders being most prevalent. Overall transition rates to psychosis were low at 24 month follow-up (2/28; 7.1%) whilst many participants demonstrated a significant reduction in psychotic-like symptoms. The generalisation of these findings may be limited due to the small sample size and require replication in a larger sample.

Keywords: psychosis, risk, youth, prodrome

Abbreviations: ARMS (At-Risk Mental State for psychosis)

Introduction

Schizophrenia-spectrum disorders are usually preceded by a prodromal period characterised by changes in thinking, perception, mood, affect and behaviour [1]. Efforts have been made to prospectively identify a state of increased risk for impending illness [2]. As this state is conceptualised as conferring a relatively increased, but not inevitable risk of illness it has been labelled as an 'At-Risk Mental State' (ARMS) for psychosis (compared to the retrospectively recognised 'prodrome'). This ARMS or 'psychosis risk syndrome' (predominately defined by the presence of one or more attenuated psychotic symptoms, occurring within the last year, leading to distress and help seeking), was proposed for inclusion in the upcoming DSM-V [3,4]. Potential benefits of this new diagnostic criteria have been highlighted [5]. However, critics of the concept argued that this diagnostic category is premature given the relatively low positive predictive value and the, as yet, unquantified risks of identifying 'false positive' cases [6,7]. Consequently the DSM working group have decided against inclusion of such a syndrome in DSM-V [8].

Within the ARMS literature, research focussing specifically on younger adolescents (<18 years) as opposed to adults and older adolescents (≥18 years) is scarce. However, identification of the ARMS in this age group should be considered a high stakes issue since young people who go on to develop psychosis generally experience worse outcomes [9,10] and describe more severe symptomatology in the form of 'negative' symptoms [11,12]. Moreover, possible signs and symptoms of the ARMS in this age group lack specificity [1] and may represent neuro-maturational and psychological changes occurring naturally during adolescence [13,14]. Subclinical psychotic symptoms also appear transitory in children [15] and adolescents [16] and are frequently reported by non-help seeking adolescent populations [17-19] although the latter is also the case in adults [20].

‘Wrongful’ identification might expose young people to unnecessary labelling and potentially hazardous pharmacological treatments [21] and use of a ‘psychosis’ related label could potentially obstruct a patient’s communicative interactions with others [22,23]. A better understanding of the presentation and characteristics of adolescents with a potential ARMS is thus crucial to informing the approach of mental health services to affected individuals.

Prospective studies of adults with an ARMS indicate that individuals present with substantial impairments in functioning, symptomatology and quality of life [24-28]. The majority of these individuals report distressing attenuated symptoms of perceptual disturbances and ideational anomalies [29-31]. Several studies report that a high proportion of those identified with an ARMS also fulfil the criteria for another Axis I mental health diagnosis, mostly relating to mood, anxiety and substance misuse [24,26,27]. Additionally, around 10% of ARMS individuals have attempted suicide shortly before presentation [32]. In terms of transition rates to psychosis a recent meta-analysis (mean age 19.9 years) estimated around 18% of such individuals develop psychosis by six months, reaching 36% after three years [33] with existing data suggesting transition is most likely within the first six months after identification [34].

Only a handful of studies have looked at the presentation of at-risk adolescents [35-38] excluding studies where risk is solely based on genetic predisposition. In one of the first studies, Meyer and colleagues [36] identified 24 adolescents who reported significant perceptual abnormalities (20/24, 83%), unusual thought content (18/24, 75%) and suspiciousness (13/54%) symptoms at baseline assessment. Twelve (50%) participants also met DSM-IV criteria for a major depressive disorder. Other co-morbidities observed included

social phobia, generalised anxiety, post-traumatic stress and eating disorders. The authors concluded that identifying adolescents with a potential ARMS is challenging given that the majority of participants met actual and sub-threshold criteria for around 3-4 mental disorders. In one of the largest studies to date Ziermans and colleagues [38] assessed 72 adolescents and discovered that the vast majority presented with impaired functioning (Mean GAF= 59.6), some form of attenuated psychotic symptoms (90.3%), but few reported a history of regular cannabis abuse (around 20%).

In terms of transition to psychosis, two adolescent-specific cohorts report transition rates of 14% and 15.6% after 18 and 24 months respectively [39,38]. The latter study also reported that 50% of participants experienced a full remission of symptoms within the outlined two year period. These findings have subsequently been confirmed in a separate study where full remission of subclinical hallucinations was apparent in 50% of participants whilst partial remission was observed in two-thirds of the 84 strong cohort [16]. A separate study reported that those who experience attenuated psychotic symptoms prior to 18 years are significantly more likely to subsequently develop psychosis [40], suggesting that studies investigating transition to psychosis should consider oversampling adolescents.

The majority of 'at-risk' studies have recruited adolescents from adult-orientated trials or retrospective patient data. Thus there has been little focus on individuals drawn from Community Child and Adolescent Mental Health Services (CAMHS). Recently published UK guidelines from the National Institute for Health and Clinical Excellence (NICE) in relation to the recognition and management of psychosis in children and young people [41], also highlights research in this age group as a priority area. The primary aim of the present study was to clinically characterise adolescents (<18 years), identified as having an ARMS,

presenting to CAMHS. A secondary aim was to report six, twelve and twenty four month outcomes in terms of transition rates and symptom levels.

Methods

Participants

A research clinic (the 'Follow-up of the At-Risk Mental State for Psychosis' - FARMS Clinic) was established (for the purposes of this study). This was hosted within an NHS Early Intervention in Psychosis (EIP) service in North-East England. The service serves an adolescent population of around 150,000 people living across a mix of rural and urban communities. The remit of the clinic was to assess adolescents fulfilling the ARMS criteria. Referrals to the clinic were only accepted from CAMHS clinicians after an initial telephone consultation with one of the research team. CAMHS clinicians were only asked to contact the clinic if a set of screening criteria were met (see Online Resource 1). Referrals were accepted if the young person was; under the care of CAMHS services; aged between 12 to 18 years of age, and; suspected of fulfilling the ARMS criteria (based upon the information supplied during the consultation). This screening process was utilised to ensure that the majority of accepted referrals would meet ARMS criteria upon further assessment as a means of effectively managing clinical time. Potential participants were excluded from study entry if they had a significant learning disability (IQ<70). Individuals became eligible for study inclusion after conducting a full clinical assessment at the FARMS clinic. Individuals subsequently identified as having an ARMS as defined by the Melbourne Ultra High risk criteria [34; see Table 1] were approached and consent sought. Subsequent care and support for those identified was provided by local CAMHS and EIP services as required.

Baseline Assessment Measures

All individuals accepted for initial assessment by the FARMS Clinic were asked to complete a battery of assessments. Assessment measures were administered by either or both

researchers (PW and PAT).

The Comprehensive Assessment of At-Risk Mental States (CAARMS) is a semi-structured interview designed specifically for the assessment of help seeking individuals suspected of having ARMS [42]. It measures a range of 'positive' psychotic like symptoms and categorises individuals using the Melbourne UHR into three potential groups (See Table 1). **Group 1** (Vulnerability Group) represents individuals who have a first degree family history of psychosis. **Group 2** (Attenuated Psychosis Group) represents individuals with either sub-threshold psychotic like symptoms based upon their lower intensity and/or frequency. **Group 3** (BLIPS Group) represents individuals experiencing intense and frequent psychotic symptoms which last no longer than a week in duration and spontaneously remitted. For all groups symptoms have to be associated with a period of declining or chronically poor functioning. Acceptable levels of inter-rater reliability between both researchers in scoring the CAARMS was demonstrated ($\kappa = 0.75$). During assessment, deterioration or chronic functioning was estimated using the Children's Global Assessment Scale (C-GAS; [43]).

In order to assess for current co-morbidity the Development and Well-Being Assessment (DAWBA) was utilised to generate ICD-10 psychiatric diagnoses [44]. Information was collected from several sources where possible, using direct observations and information from the young person, their medical notes as well as parental and/or teacher reports. To ensure a rigorous methodological approach to diagnosis, principles of the best estimate procedure were adopted [45] whereby both researchers were kept blind as to each other's decisions until a diagnostic review meeting was undertaken (also involving the young person treating clinician). Diagnostic decisions and confirmation of an ARMS were made via

consensus between all group members.

Other assessment tools utilised in order to improve diagnostic categorisation and record symptom profiles included the Young Mania Rating Scale [46] and Hamilton Depression Rating Scale (HAM-D; [47]). The Social & Communication Disorder Checklist was used as brief screening measure for pervasive developmental disorders [48].

[Insert Table 1 here]

Follow-up Assessment measures

Where possible, individuals were assessed using the CAARMS and the C-GAS. Medical notes and information obtained from the young person's treating clinician were also reviewed to assess for the possibility of psychosis transition, symptom and ARMS remission and to record interventions offered by CAMHS and EIP services within the intervening period. Psychosis transition was defined by CAARMS scores above the threshold stipulated for ARMS identification (Table 1) alongside the initiation of anti-psychotic medication. In addition, individual presentations had to fulfil the ICD-10 diagnostic criteria for schizophrenia or a related disorder (e.g. delusional disorder) in order to be deemed to have transitioned to psychosis. Thus, psychosis transition would be established via information from medical records and treating clinicians, and where possible, direct assessment via face-to-face or telephone interview.

Data Analysis

Data analysis was predominately descriptive in nature although appropriate non-parametric statistical tests were employed to assess for significant differences between baseline and

follow-up assessment measures and other measures where required (e.g. Wilcoxon signed-rank test, Chi square and Fisher's exact tests).

Ethics and ethical considerations

Ethical approval for the study was granted by Durham University, School of Medicine and Health Ethics Committee and the NHS National Research Ethics Service for County Durham & Tees Valley. Informed written consent was obtained from all participants. In the case of younger adolescents (those below 14 years), consent was also obtained from a parent/carer. Consent was also taken in advance for permission to contact participants and review medical notes at the subsequent follow up stages. For individuals who went on to develop psychosis, the follow up assessment regimen was adjusted to accommodate for their present psychiatric condition.

Results

Demographics

Thirty-eight adolescents were assessed by the FARMS clinic between January 2010 and April 2011, with 30 individuals identified as fulfilling the ARMS criteria and consenting to study participation. Of those not meeting intake criteria for the study; three were already psychotic at the time of the assessment, three disengaged halfway through the assessment process whilst two were deemed to be below the symptom threshold required for an ARMS. The mean age of the ARMS sample was 15.8 years (s.d. = 1.4) whilst the sex distribution was relatively even (Female=16/30, 53%). All participants were of a White British ethnic origin (which reflects the lack of ethnic diversity locally) and met the criteria for Group 2 (Attenuated Psychosis Group) of the Melbourne UHR criteria. Of these, four individuals also had a family history of psychosis (Group 1; Vulnerability Group).

'Positive' symptomatology

The majority of participants presented with some form of auditory perceptual disturbances (27/30; 90%) although Bizarre ideas, Visual Changes and Suspiciousness/Persecutory Ideas were also commonly experienced. Ninety percent (27/30) of individuals reported co-occurring perceptual disturbances alongside delusional ideation.

Global rating, frequency and duration and associated distress scores for positive symptoms as measured by the CAARMS are outlined in Table 2. These suggest that *Perceptual Abnormalities* were the most intense and distressing symptoms experienced within the cohort whilst symptoms of *Disorganised Speech* indicate a picture of relatively low intensity and distress.

[Insert Table 2 here]

ICD-10 co-morbid conditions

In total 21/30 (70%) participants were found to meet the threshold for at least one current ICD-10 Axis I diagnoses. Individuals were most likely to meet the criteria for a depressive illness (13/30; 43%), anxiety disorders (6/30; 20%) or pervasive developmental disorders (5/30; 17%). The high levels of depressive illness are reflected in the mean overall HAM-D scores (10.9; s.d.=6.4) which indicate a mild severity considered to be outside the normal population range. Further analysis of depressed individuals, indicated that these participants were less likely to report Suspiciousness/Persecutory Ideas ($\chi 2$= 4.434, p= .035) but experienced more distressing symptoms of *Unusual Thought Content* (z= -2.18, p= .031) and *Perceptual Abnormalities* (z= -2.25, p= .025). The co-morbid data analysis also indicates that reported substance abuse (prior and current alcohol and illicit drug use) within the sample was low. Seven of the 30 participants (23%) were found to have two current co-morbid ICD-10 Axis I diagnoses.

[Insert Table 3 here]

As well as meeting the threshold for an Axis I diagnosis many participants were recorded as experiencing sub-threshold difficulties. These were defined as symptoms that did not reach the threshold for an Axis I diagnosis using ICD-10. This was because they were deemed to be secondary to (and potentially caused by) the primary Axis I diagnosis or were not detrimental to the person's functioning at that time. The most frequent of these sub-threshold symptoms appeared to be obsessive compulsive symptoms (10/30; 33%), depression (9/30; 30%) and

abnormally elevated or irritable mood ('Mania'; 9/30; 30%). Also within this cohort, a high proportion of individuals reported having attempted suicide (9/30; 30%) or had engaged in significant self-harm (16/30; 53%) within the previous six month period.

Six month outcomes

It was possible to establish the current mental state for 29/30 (97%) participants at six months. Only one participant had become psychotic during the previous six months (1/29; 3.4%). This individual was male, had experienced paranoid and multi-sensory perceptual experiences for a duration of at least one month prior to follow-up and was subsequently diagnosed with Schizophrenia, unspecified (ICD-10 code; F20.9). Seven of the remaining twenty-eight individuals no longer fulfilled criteria for an ARMS (7/28; 25%). In terms of symptomatology, there was a significant remission in the presence of *Visual Changes* ($\chi 2$= 5.371, p= .02) and *Disorganised Speech* ($\chi 2$= 10.286, p= .01) as well as a significant improvement in C-GAS scores (z =-2.811, p =.005) at the six month stage. A list of interventions offered after identification indicates that participants received a variety of interventions for their psychotic-like symptoms.

[Insert Table 4 here]

Twelve and twenty-four month outcomes

Due to the withdrawal of consent by two participants and the refusal of several participants to engage in follow-up CAARMS assessments, follow-up analysis mainly relied upon inspection of medical records and clinician information. Data indicated that 3/29 (10%) had been lost to follow-up at the twelve month stage making it impossible to establish their current mental state. At this time point, no further individuals had made the transition to

psychosis, although many remained in contact with mental health services (16/26; 62%), mainly due to reported depressive symptoms and/or sub-threshold psychotic symptoms (Table 5). At the twenty-four month stage, one participant originally lost to follow-up at the six and twelve month assessment points, returned to services due to admittance to an accident and emergency department as a result of an overdose. There was evidence from medical records that one additional participant had become psychotic. This assertion is based upon the reporting of persistent and distressing auditory and visual hallucinations by the participant to the treating clinician, as recorded in their medical notes. Moreover, treatment with an antipsychotic (quetiapine) was instigated specifically for these symptoms. It was clear from the psychiatric notes that the treating clinician considered these phenomena as indicative of a psychotic illness. This event took the overall observed transition rate in this cohort to 2/28 (7.1%). However, some caution should be exercised in assuming this latter transition event as the participant had declined a face-to-face interview at this point in the follow-up. Thus direct assessment and verification of illness status was not possible.

[Insert Table 5 here]

Discussion

The findings indicate that adolescents with an ARMS present to mental health services with significant levels of impairment. These findings are comparable to those observed in other studies predominately consisting of older adolescents and adults [25,29-31]. In terms of symptomatology perceptual abnormalities, especially auditory hallucinations are the most frequent, distressing and severe 'positive symptoms' experienced by adolescents. These findings are supported by one other adolescent specific study [36] but not by those recruiting adult samples [30,25] who report more prevalent symptoms of suspiciousness and non-bizarre ideas. It has been postulated that hallucinatory experience may give rise to secondary delusional interpretation, thus increasing the risk of psychosis transition [49]. For example, the mere experience of voices itself does not lead to full-blown psychotic symptoms, but attributing the voice to an external source and giving it personal significance does [50]. Despite this, in our sample there was virtually no early transition to psychosis evident. This is possibly because these auditory disturbances may have been more dissociative in nature, as opposed to being related to a psychotic illness. Such dissociative experiences are known to commonly occur in non-clinical samples of adolescents [51].

In line with previous findings, co-morbidity at presentation to services was the norm, with depression and anxiety disorders frequently observed [24,26,35,36,27]. Interestingly, individuals with co-morbid depression experienced more perceptual disturbances and unusual thought content, suggesting the existence of a sub-group of ARMS individuals. In contrast, high rates of Pervasive Developmental Disorder are not reported by studies recruiting mainly working-age adults. This may reflect the ability of child and adolescent services to identify developmental disorders [52] or the reduction of detectable autistic symptoms with age and

maturation. Indeed within adolescent ARMS populations, PDD may be prevalent given its probable association with juvenile-onset schizophrenia [53].

Our observed short-term transition rate of 3.4% and longer-term rate of 7.1% is low compared to those reported by a recent meta-analysis (18% at six month and 29 % at two years; [33]) and other adolescent studies published to date [38,39]. Thus, our findings do not support the view that adolescents are significantly more likely to make the transition to psychosis compared to older individuals [40]. The observed reductions in visual hallucinations, disorganised speech and improvements in psycho-social functioning at six months also indicate that adolescents may experience more transitory subclinical psychotic symptoms [16] compared to adults, making prediction of transitions to illness more challenging. Thus, this small sample of particpants may have included a significantly high number of 'false positive' cases (those who were never at risk of psychosis). Other explanations for these disparities include swift and effective access to treatments (due to the establishment of this assessment clinic) which ultimately delayed or prevented psychosis transition. In spite of the transitory nature of psychotic-like symptoms, many adolescents appear to remain in clinical contact with mental health services twelve month post identification, although this appears in order to receive on-going support for other difficulties such as depression, anxiety and self-harm.

To the authors' knowledge this is the first study to prospectively characterise and assess the short term outcomes of adolescents with an ARMS within the UK. Despite the 'hard to reach' nature in recruiting adolescent populations, the sample size of 30 individuals is small (especially in comparison to the recent EDIE-2 treatment trial; n=288 [25]) and was thus underpowered to robustly explore putative predictors of transition. Moreover, the small

numbers of participants and limited sampling frame (e.g. a section of NE England) limits the generalisability of these findings to other clinical populations. Future research should therefore adopt multi-site designs in order to validate our findings in this patient group. Larger samples may also permit statistical identification of symptom clusters in order to validate distinct sub-groups of patients, for example via latent class analysis. Understanding how this patient group differs to other adolescents psychiatric help-seekers, via a case-control study design, would be useful in comparing short to medium term clinical outcomes and symptom profiles. Moreover, an analysis of 'positive' symptom clusters across co-morbid conditions, the use of a validated screening tool (such as the PROD screen, [54]) at the telephone referral stage and the recording of previous treatment history would have improved the present study design.

The varied symptom and co-morbidity profiles observed in adolescents, combined with potentially low transition rates and high levels of symptom remission may result in increased apprehension regarding the categorisation of younger adolescents as having an ARMS. Indeed, it has been postulated that at times psychotic-like symptoms may represent 'clinical noise' around a non-psychotic syndrome [55]. Regardless of this the high levels of distress and impairments our participants reported suggest that these individuals require some form of support from services. Treatment could target distressing symptoms and aim to improve psychosocial functioning. Indeed, these may be more of an issue than the risk of transition to psychosis [56]. In order to manage therapeutic resources and reduce any adverse effects of wrongful identification, it may be sensible to initially offer individuals the least invasive interventions possible (i.e. psycho-education, solution focussed therapy). Our data may indicate that individuals who do not experience symptom or functional remission from an ARMS after six months, should then be offered a more intensive form of psychological

intervention (i.e. CBT). Given our findings, a move away from measuring transition as a primary outcome and a focus upon symptom remission and functional improvement maybe sensible.

Summary

As in adults, young adolescents fulfilling the ARMS criteria present to mental health services with high levels of non-specific psychopathology, impaired functioning and distress. However, the low transition rate and high levels of symptom remission (even over a short term period) not only questions the validity of these criteria to predict future psychosis but may highlight a more fluctuating symptomatic state in this younger population. These putative differences should be taken into account when designing services for younger populations presenting with the clinical picture of an ARMS.

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